HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN FOR THE

SORBITAN ESTERS CATEGORY OF THE

ALIPHATIC ESTERS CHEMICALS

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

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EXECUTIVE SUMMARY

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) hereby submits a revised test plan for the "sorbitan esters" category of the "aliphatic esters" chemicals, under the High Production Volume (HPV) Chemical Challenge Program. The Panel has used existing available public and company data in conjunction with scientific judgment/analysis to characterize the Screening Information Data Set (SIDS) of human health, environmental fate and effects, and physicochemical property endpoints for the sorbitan esters category.

This test plan addresses six HPV sorbitan esters substances listed in Table 1A. These six HPV substances have the distinguishing chemical feature that sorbitan comprises the alcohol portion in the esters. Sorbitan is derived from the naturally occurring carbohydrate sugar, sorbitol, and has four hydroxy groups available in its structure for esterification. The acid portion of the HPV sorbitan esters is comprised mainly of natural fatty acids (e.g., lauric, stearic and oleic acids, coconut oil fatty acids). Four of the HPV substances are sorbitan monoesters while the other two HPV substances have multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). Three of the HPV substances (i.e., the oleate esters of sorbitan) are essentially the same except for their degree of esterification.

The chemical and structural similarities of the sorbitan esters listed in Table 1A justify grouping these six HPV chemicals together under the sorbitan esters category of the aliphatic esters. They have close commonalties in their physicochemical properties, chemical characteristics and biological/toxicological activities as a result of the structural similarities (e.g., sorbitan and natural fatty acids) in their molecules. Grouping these sorbitan esters together also represents a rational structural approach: (1) to systematically compare existing data; (2) to justify read-across assessments for structurally related sorbitan esters, and (3) to develop a stepwise strategy test plan for the sorbitan esters substances based on their ester group type. The sorbitan esters as an ester group type are structurally differentiated from other aliphatic ester group types such as the diesters, polyol esters, and glycol esters.

In addition to the available data for the HPV sorbitan esters in this category, there were unpublished data available for one structurally analogous surrogate sorbitan ester [namely, sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5)] that provided useful supplementary information to help toxicity data bridging for the structurally related HPV sorbitan esters. Sorbitan fatty acid esters are non-ionic surfactant-active agents that typically are used as emulsifiers, stabilizers and thickeners in foods, cosmetics, medical products, lubricants and other applications. Some of the HPV sorbitan esters are approved for use in cosmetic and pharmaceutical applications. Consequently, a substantial amount of toxicity data and health and safety information exist for the HPV sorbitan esters and for many structurally analogous sorbitan fatty acid esters. Much of the available health and safety data have been peer reviewed by the Cosmetic Ingredient Review expert panel.

Calculated physicochemical properties data were available for the HPV and surrogate sorbitan esters and were supplemented with measured values. In addition, computer estimation models were used to calculate environmental fate data for the sorbitan esters. The calculated data were obtained using the EPIWIN and EQC (Level III) models that EPA has cited for use in the HPV Chemical

Challenge Program. Use of the experimental and calculated values provided the information on the physicochemical and environmental fate properties of the substances in the sorbitan esters category to satisfy HPV program requirements. No additional testing for physicochemical and environmental fate properties is proposed for the sorbitan esters category of the aliphatic esters.

Adequate aquatic toxicity and biodegradability data exist for both the HPV sorbitan esters and one structurally analogous surrogate sorbitan ester to sufficiently cover the range of sorbitan esters within in this category. The very close structural and chemical similarities between the homologous sorbitan esters within this category reasonably justify and support read-across assessments among the HPV substances. No further aquatic toxicity and biodegradability testing are proposed for the sorbitan esters category of the aliphatic esters.

The available data on the mammalian toxicity or health effects (i.e., acute, repeated dose, genetic toxicity, reproductive/developmental effects) from both HPV substances and a structurally analogous surrogate substance were adequate to cover the SIDS data endpoints for the range of sorbitan esters in this category and to permit read-across assessments. No additional mammalian toxicity testing is proposed for the sorbitan esters category of the aliphatic esters. This resourceful use of the existing data will help to minimize the use of animals for testing while assessing the potential hazards of the substances in the sorbitan esters category under the HPV Chemical Challenge Program.

The following member companies of the American Chemistry Council's Aliphatic Esters Panel are sponsoring the Sorbitan Esters category:

BASF Corporation

Cognis Corporation

Uniqema Corporation

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TEST PLAN FOR THE SORBITAN ESTERS CATEGORY OF THE ALIPHATIC ESTERS

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) has committed voluntarily to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and human health effects) for the Sorbitan Esters category of aliphatic esters chemicals, listed under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program.

This test plan sets forth how the Aliphatic Esters Panel intends to address the testing information for the six sorbitan esters listed in Table 1A (organized by CAS Numbers). The chemical structures of the sorbitan esters are given in Figure 1. The chemicals in the test plan were originally part of a larger test plan submitted on December 20, 2001. As a result of public comments, the Panel has revised its original test plan for these chemicals, and the revised approach follows below.

The test plan identifies the CAS Numbers used to characterize the SIDS endpoints for the sorbitan esters in this category, describes the chemical and structural features/similarities of the sorbitan esters, identifies existing data of adequate quality for substances in the sorbitan esters category, and provides the Panel's rationale for applying the available SIDS data to characterize the hazards of the category members. The primary objective of this effort is to identify and characterize the physicochemical properties, mammalian health and environmental fate and effects for the sorbitan esters category of the aliphatic esters consistent with the EPA HPV Program.

Developing a data matrix with reliable studies and applying justifiable read-across assessments will help provide a sufficiently robust data set to characterize the endpoints in the HPV Chemical Challenge Program. This approach to the resourceful use of existing data will help minimize the use of animals for testing while assessing the potential hazards in the sorbitan esters category of the aliphatic esters.

Table 1A: List of Individual Substances in the Sorbitan Esters Category
(by ascending CAS Numbers and designated TSCA HPV chemical name)

Chemical Name (designated TSCA HPV chemical name)	**CAS Number**
Sorbitan, monolaurate	1338-39-2
Sorbitan, monostearate	1338-41-6
Sorbitan, monooleate	1338-43-8
Sorbitan, sesquioleate	8007-43-0
Sorbitan, trioleate	26266-58-0
Fatty acids, coco, monoesters with sorbitan	68154-36-9

2.0 DESCRIPTION OF THE SORBITAN ESTERS CATEGORY

Six CAS Numbers are used to describe the sorbitan esters in this HPV category of the aliphatic esters (Table 1A). Chemically, the sorbitan esters category is comprised of substances that are ester derivatives of sorbitan (which is derived from sorbitol - a natural carbohydrate sweetener) and monoacids (derived from natural fatty acids). The natural fatty acids may include lauric, stearic, oleic acids and coconut fatty acids (mainly lauric and myristic acids). Thus, sorbitan esters can be regarded as carbohydrate-derived esters with ester linkage(s) to the hydroxy group(s) of sorbitan. Although there are four hydroxy groups in sorbitan available for esterification, most of the sorbitan esters on the HPV list are monoester derivatives. Four of the substances in the HPV sorbitan esters category are monoester derivatives of sorbitan. The other two substances, sorbitan sesquioleate and sorbitan trioleate, contain multiple ester linkages. The greater the degree of esterification with long-chain fatty acids would be expected to increase the lipophilicity and diminish the water solubility of the sorbitan esters. Three of the HPV substances [i.e., sorbitan monooleate, sorbitan sesquioleate and sorbitan trioleate] can be regarded to be chemically similar (i.e., sorbitan and oleate) except for the degree of esterification.

Sorbitan fatty acid esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers and thickeners in foods, cosmetics, medical products, lubricants and other applications [Andersen (2002); Eisenhard (1999)]. Some of the HPV sorbitan esters are approved for use in cosmetic, food and pharmaceutical applications. Consequently, a substantial amount of toxicity data and health safety information exist for the HPV sorbitan esters and for many structurally analogous sorbitan esters. Sorbitan esters, including the HPV substances, have low orders of toxicity as will be discussed in Section 4 of this test plan. Extensive amounts of toxicity data exist for the sorbitan esters in the literature. Safety assessments and comprehensive mammalian toxicity reviews for a large number of sorbitan fatty acid esters have been carried out by Cosmetic Ingredient Review Expert Panel [CIR (1999)] and published in the Journal of the American College of Toxicology and the International Journal of Toxicology [Elder (1985); Andersen (2002)]. Toxicity profile reviews for sorbitan monostearate and sorbitan trioleate have also been reviewed by BIBRA [BIBRA (1990, 1994)]. It is beyond the scope of this test plan to review in detail all the toxicity data reported for the various sorbitan esters except to note that the literature is quite extensive and has been comprehensively reviewed elsewhere [Elder (1985); CIR (1999); Andersen (2002)].

In addition to the wealth of peer-reviewed safety data, sorbitan esters have been used as emulsifiers and thickeners in food applications. History with these applications provides evidence that they generally do not represent a health safety concern. They are synthesized from naturally occurring substances and the parent esters can undergo metabolism (via enzymatic hydrolysis) back to these same natural constituents, namely, sorbitan and fatty acids, both of which have low orders of toxicity. Sorbitan (CAS 12441-09-7) is listed in the FDA/CSFAN database as an indirect food additive. Naturally occurring fatty acids like lauric, myristic, stearic, oleic acids and coconut oil fatty acids are expected to have very low orders of toxicity [Andersen (2002); Elder (1986, 1987); Cragg (2001 a,b); HPV (2001)].

Metabolism of the sorbitan esters in animals has been reported to occur initially via enzymatic hydrolysis, leading to sorbitan and the corresponding natural fatty acids. Oral gavage studies in rats

with radiolabelled sorbitan monostearate (administered in oil solution) have demonstrated that about 90% of the sorbitan monostearate dose was absorbed and hydrolyzed to stearic acid and sorbitan [Elder (1985); Wick (1953)]. These findings would suggest that other sorbitan fatty acid esters may undergo similar enzymatic hydrolysis when orally ingested and they would be expected to be metabolized to sorbitan and the corresponding fatty acids. The resulting sorbitan and fatty acid metabolites, in turn would be expected to be metabolized further (via fatty acid beta-oxidation or carbohydrate metabolic pathways) to either smaller and more polar water-soluble metabolites excretable in the urine or as carbon dioxide exhaled in the lungs.

Metabolic hydrolytic reactions of various esters have been extensively reviewed in the literature [Testa and Mayer (2003); David *et al.* (2001); Buchwald (2001); Parkinson (2001); Satoh *et al.* (1998); Heyman (1982)]. It is beyond the scope of this test plan to discuss or review this topic in more detail except to mention its contribution in the general metabolism scheme for ester linkages.

Organization of HPV and Surrogate Sorbitan Esters Substances by Molecular Weight

As will be discussed in Section 4, in addition to the existing available data for the six HPV sorbitan esters in this category, there were unpublished toxicity data available for one structurally analogous surrogate sorbitan ester, namely, sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5), which provided useful read-across information to help bridge data needs.

To help facilitate data evaluation, it is useful to organize the 6 HPV and the one surrogate sorbitan esters according to ascending molecular weight (MW) rather than in the order of their CAS numbers as in Table 1A. The arrangement of the substances based on molecular weight (MW) (as a reflection of their fatty acids and the degree of esterification) will be useful in comparing and visualizing chemical /structural similarities among the analogous series of sorbitan fatty acid esters in this category. It also will provide a rational and systematic basis for using existing read-across data and to bridge data needs among structurally analogous or homologous sorbitan esters in this series. Table 1B organizes the sorbitan esters in that manner.

Table 1B. Six HPV Sorbitan Esters and One Surrogate Sorbitan Ester Organized According to Molecular Weight (MW)

Individual Sorbitan Esters (arranged according to MW) Chemical Name (designated TSCA HPV names)	CAS Number	Carbon Number in Acid	Carbon Number in Sorbitan	Total carbons in Ester	MW
Sorbitan, monolaurate	1338-39-2	C12	C6	C18	346
Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	68154-36-9	C12 to C14	C6	C18 to C20	346-374
Sorbitan, monooleate	1338-43-8	C18	C6	C24	429
Sorbitan, monostearate	1338-41-6	C18	C6	C24	431
Sorbitan, sesquioleate	8007-43-0	C18	C6	C33	569
* Sorbitan, fatty acids C6-10, tetraester	228753-47-5	C8**	C6	C38	668
Sorbitan, trioleate	26266-58-0	C18	C6	C60	958

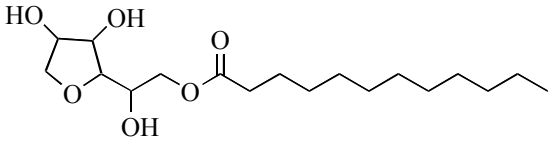
* Shaded or highlighted row denotes one surrogate sorbitan ester that was not part of the HPV sorbitan esters test plan. However, it was included in this matrix table since existing toxicity data for this surrogate substance were useful for read-across assessment or for bridging data to other sorbitan esters category members based on their chemical /structural similarities.

** The average carbon number of fatty acid is C8 for sorbitan, fatty acids C6-10, tetraester.

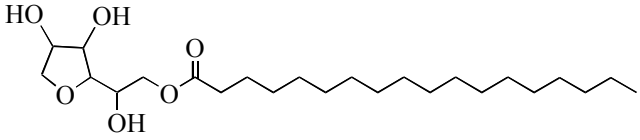
Figure 1 Chemical Structure of the Sorbitan Esters Listed in Table 1A

The structures of the HPV sorbitan esters are given in the order listed in Table 1A, which are organized according to ascending CAS Numbers. The chemical structure depicted for each HPV substance is consistent with the designated CAS Number and is considered representative of the commercial product evaluated.

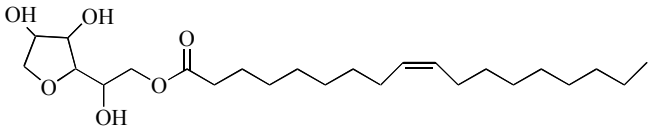
Sorbitan, monolaurate (CAS 1338-39-2)



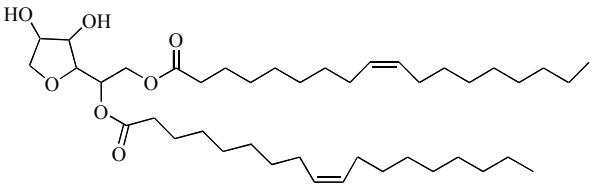
Sorbitan, monostearate (CAS 1338-41-6)

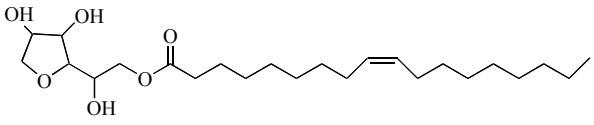


Sorbitan, monooleate (CAS 1338-43-8)

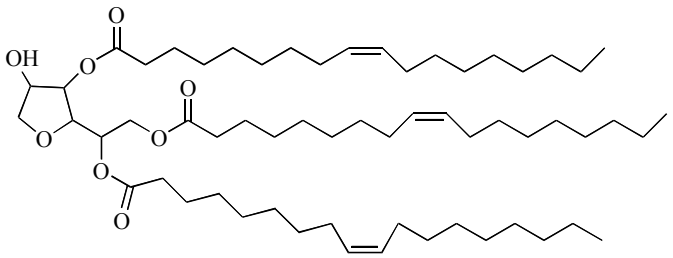


Sorbitan, sesquioleate (CAS 8007-43-0)
is mixture of monooleate and dioleate (~1:1 ratio)





Sorbitan, trioleate (CAS 26266-58-0)



Fatty acids, coco, monoesters with sorbitan (CAS 68154-36-9)

(shown are the lauric and myristic fatty acid ester derivatives)

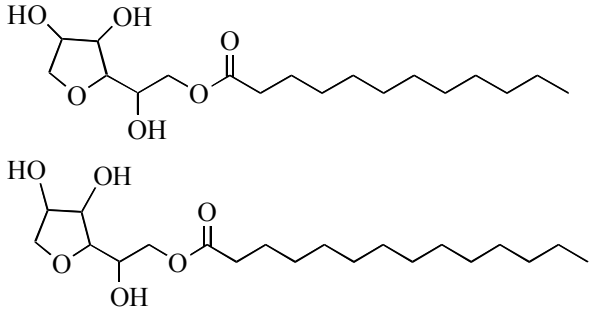
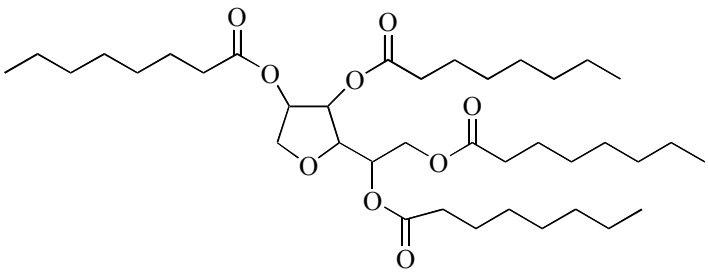


Figure 2. Chemical Structure of Surrogate Sorbitan Esters Substance

Sorbitan, fatty acids, C6-10, tetraester (CAS 228753-47-5)
(shown is C8 fatty acid, average carbon number of fatty acid)



3.0 DESCRIPTION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and company data was conducted on the physicochemcial properties, mammalian toxicity endpoints, and environmental fate and effects for the six sorbitan esters using CAS numbers and chemical names. Searches included the following sources: MEDLINE, TOXLINE and RTECS databases; the TSCATS database for relevant unpublished studies on these chemicals; standard handbooks and databases (e.g., Sax, CRC Handbook of Chemistry and Physics, IUCLID, Merck Index, etc.) and other references for physicochemical properties.

The reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive reviews [e.g., Patty's Toxicology (2001)]. Safety assessments and comprehensive mammalian toxicity reviews for a large number of sorbitan fatty acid esters have been carried by Cosmetic Ingredient Review (CIR) expert panel [CIR (1999)] and published in the Journal of the American College of Toxicology and the International Journal of Toxicology [Elder (1985); Andersen (2002)]. Sorbitan esters that are structurally analogous or related (i.e., homologs, similar carbon number or molecular weight range) to the HPV sorbitan esters were also reviewed to determine whether they were relevant for bridging data needs for environmental fate, aquatic toxicity or mammalian toxicity. The existing toxicology reviews by the CIR on numerous relevant sorbitan esters were especially useful for assessing the HPV sorbitan esters [Elder (1985); CIR (1999); Andersen (2002)].

3.1 Physicochemical Properties Data

Physicochemical data [i.e., melting point, boiling point, vapor pressure, water solubility and octanol water partition coefficient (kow)] for the HPV and the surrogate sorbitan ester were obtained from the searches and sources described above. In addition to available experimental and measured data, calculated physicochemical values were also incorporated into a summary table for all these physical and chemical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements.
- A complete set of physical property data was a prerequisite to calculate fugacity or the chemical distribution in the environment (see below).
- Physicochemical properties data had yet to be developed for some of the sorbitan esters.

The physicochemical properties were calculated using the Syracuse Research Corp./EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed for the EPA [EPIWIN (1999); US EPA (1999b)]. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model, a specific discreet structure is required. EPIWIN contains a CAS number database that contains the structures for a large number of chemicals. For mixtures, a single representative structure is contained in the database and in this test plan, these surrogate chemical structures were accepted for further modeling.

3.2 Environmental Fate and Biodegradability Data

Environmental fate data including biodegradability, photodegradation, stability in water (i.e., hydrolysis) and fugacity (chemical distribution in the environment) data were primarily obtained through the literature, from unpublished company data, or from modeling [e.g., EPIWIN, EQC (Level III) - Mackay *et al*. (1996)]. When relevant studies (particularly biodegradability endpoints) were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch *et al*. (1997) was utilized to evaluate the data quality of the studies.

3.3 Aquatic Toxicity Data

Existing data for aquatic toxicity studies (e.g., fish, invertebrate and algae) for the HPV and surrogate sorbitan esters were obtained primarily from the literature or from unpublished company studies. When relevant studies were identified, the study reports were reviewed, robust summaries were prepared and the reliability of the data was assessed. The method of Klimisch *et al.* (1997) was utilized to evaluate the data quality of the aquatic toxicity studies.

3.4 Mammalian Toxicity Data

The existing data for the mammalian toxicity endpoints for the HPV sorbitan esters were reviewed using the literature searches to identify the most relevant studies for the substances in the sorbitan esters category. For the HPV sorbitan esters that contained relevant data, the available studies were reviewed using the criteria outlined in the EPA's methods for determining the data quality and the adequacy of the existing data and the reliability ranking method of Klimisch *et al.* (1997). Relevant studies that were available for the mammalian toxicity endpoints are summarized in the HPV test plan and presented in greater detail in the robust summaries in the Appendix**.**

Studies that were selected for the robust summaries represented those identified as the most relevant or reliable data for the specific SIDS endpoints. Published studies from the general literature as well as from a number of unpublished company reports were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of limited experimental details to assess their quality (i.e., not assignable, Klimisch reliability code 4) or only were reported as LD_{50} values from secondary sources. These studies were included in the summary data table and may be included in the robust summaries with reference to the secondary literature source.

4.0 EVALUATION OF EXISTING DATA

The six HPV substances in Table 1A were grouped together under the sorbitan esters category since they form a series of structurally related or analogous esters comprised of sorbitan and natural fatty acids. In addition to the existing data for the six HPV sorbitan esters, there were read-across data for one structurally analogous sorbitan ester not on the HPV list. Because of its structural similarity with the HPV substances, this surrogate substance, namely, sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5), provided useful data for bridging toxicity information for structurally analogous HPV sorbitan esters.

Existing studies for the HPV and the surrogate sorbitan ester have been reviewed. Discussion will be provided in this section in regards to: the available data for SIDS toxicity endpoints, an assessment and summary of the data, and comments on HPV test plan as to whether the existing data are adequate for that purpose and whether further testing is proposed. The order of discussion of endpoints will be: (1) the physicochemical properties, (2) environmental fate and biodegradability, (3) aquatic toxicity, and (4) mammalian health effects.

4.1 Physicochemical Properties Data

Summary of Physicochemical Properties Data

Physicochemical properties (i.e., melting point, boiling point, vapor pressure, water solubility and kow) were calculated using EPIWIN for the HPV and surrogate sorbitan esters and have been summarized in Table 2. In addition, experimental physicochemical properties data (measured or those reported in studies, company documents, reference handbooks, secondary literature) have been summarized in Table 2.

Data Assessment and Test Plan for Physicochemical Properties

The HPV sorbitan esters covered the carbon-number range from C18 to C60. This reflects the range of fatty acids [C12 (lauric) to C18 (stearic and oleic)] and the degree of esterification in these materials. The chain-length of the fatty acids in the sorbitan monoesters would be expected to influence water solubility, boiling point and lipophilicity as observed from the calculated values in Table 2. The degree of esterification (monooleate *versus* trioleate) will also influence these properties. Hence, the water solubility of sorbitan monolaurate (C12 acid) (CAS 1338-39-2) was predicted to be much greater than that of sorbitan monostearate or sorbitan monooleate (C18 fatty acids). The monooleate was predicted to have greater solubility in water than the corresponding sesquioleate or trioleate esters of sorbitan.

Based on the summarized data in Table 2, for purposes of the HPV Program, adequate calculated and measured physicochemical data exist for substances in the sorbitan esters category and no further testing for these endpoints is proposed.

4.2 Environmental Fate and Biodegradability Data for Substances in the Sorbitan Esters Category

Summary of Environmental Fate and Biodegradability Data

The environmental fate and biodegradability data relevant to the sorbitan esters category are summarized in Table 2 and Table 3, respectively. Biodegradability data have been reported for sorbitan esters that cover the C18 to C38 range (Table 3).

Other environmental fate endpoints such as photodegradation, stability in water (hydrolysis) and chemical distribution (transport) in the environment (fugacity modeling) have been calculated for the sorbitan esters using the EPIWIN and EQC (Level III) models. EPIWIN calculated hydrolysis half-lives and atmospheric photodegradation rates for the sorbitan esters are summarized in Table 2. The calculated values for the transport (or distribution) in the soil, air, water and sediment environmental compartments using the fugacity-based EQC model are also summarized in Table 2.

Data Assessment and Test Plan for Environmental Fate and Biodegradability

Biodegradation data for two HPV substances [i.e., sorbitan monolaurate (CAS 1338-39-2), sorbitan monooleate (CAS 1338-43-8)] and the surrogate material [sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5)] have been reported. These three sorbitan esters were biodegraded to the extent of 60-83% in 28-days, which indicate these materials undergo extensive biodegradation in the aerobic environment. The sorbitan esters tested covered the range of carbon numbers (C18-C38) and included relatively water-soluble (i.e., sorbitan monolaurate) as well as water-insoluble [i.e., sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5)] members of the group. The high degree of biodegradation (83.1% in 28 days) for the sorbitan tetraester (CAS 228573-47-5), in spite of its poor water solubility, indicates that enzymatic cleavage of the multiple ester linkages (to corresponding fatty acids and sorbitan) is likely to be occurring in order to achieve the high extent of biodegradation observed (60-83%). This would also be consistent with the fact that fatty acids such as lauric, myristic, oleic, stearic acid (arising from microbial hydrolysis) have been shown to be rapidly and extensively biodegraded (Vershueren, 1996; Swisher, 1987). It is also reasonable to expect the family of oleate esters of sorbitan to be extensively biodegraded since microbial hydrolysis of the ester linkage in sorbitan trioleate and sesquioleate would lead to sorbitan monooleate, for which there is known biodegradation information.

There are adequate biodegradability data reported for the sorbitan esters that cover the most of the carbon numbers and MW for the substances in this category. Overall, sorbitan esters have been shown to be extensively biodegraded (>60% in 28 days). In addition, the very close structural and chemical similarities among the homologous sorbitan fatty acid esters (e.g., lauric, myristic, stearic acid series; the oleate ester family series) in this category would reasonably justify and support read-across assessments. The existing biodegradability data should be adequate to address the potential biodegradability of the members of the "sorbitan esters" category and, therefore, no additional biodegradation testing is proposed.

Other environmental fate parameters (i.e., photodegradation, hydrolysis and chemical distribution in environment) have been calculated using the EPIWIN and EQC (Level III) modeling programs. Based on the calculated data for these environmental fate endpoints in Table 2, for purposes of the HPV Program, adequate data exist and no additional testing is needed for substances in the sorbitan esters category.

4.3 Aquatic Toxicity Data for Substances in the Sorbitan Esters Category

Summary of Aquatic Toxicity Data

Aquatic toxicity studies for the HPV and surrogate sorbitan esters are summarized in Table 3. In addition, acute aquatic toxicity LC50 or EC50 values in fish, daphnia and algae have been calculated for the HPV substances using the ECOSAR model in EPIWIN [EPIWIN (1999); US EPA (1999b)]. The ACC Aliphatic Esters Panel believes that, collectively, the experimental and calculated ecotoxicity data are sufficient to address the sorbitan esters in this category or to reasonably justify read-across assessments to bridge data based on the structural and chemical similarities of these sorbitan fatty acid esters.

Data Assessment and Test Plan for Aquatic Toxicity

Aquatic toxicity data have been reported for the sorbitan esters. Two HPV substances, sorbitan monolaurate and sorbitan monooleate, have been tested. In the case of sorbitan monolaurate, no mortality was reported in rainbow trout at nominal concentrations of 10, 18, 32 and 56 mg/L. Mortality, however, was observed at 100 mg/L and the LC50 value was estimated to 75 mg/L for this substance. Sorbitan monooleate (CAS 1338-43-8) caused no mortality in rainbow trout at nominal levels of 1000 mg/L in an acute 96-hr fish toxicity study. The calculated water solubility of sorbitan monooleate was 0.0191 mg/L. Thus, it appears that sorbitan monooleate ester would not be expected to cause acute toxicity at its water solubility limit (WSL).

The surrogate substance, sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5), also has been evaluated in fish, daphnia and algae. The LC50 or EC50 value was reported to be greater than 1000 mg/L [nominal loading concentrations in the water accommodated fraction (WAF) solutions tested] in all three aquatic species for this structurally analogous surrogate. The measured water solubility of sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5) was <0.02 mg/L, which would suggest that this surrogate sorbitan ester would not be expected to cause acute aquatic toxicity at its water solubility limit (WSL).

Because sorbitan sesquioleate and sorbitan trioleate comprise the oleate family of sorbitan esters (i.e., multiple ester linkage with oleic acid), it seems reasonable that these substances would also be expected to show a similar low degree of aquatic toxicity as reported for sorbitan monooleate. As a result of the greater degree of esterification in the sesquioleate and trioleate, they are clearly more lipophilic and less water-soluble than the corresponding sorbitan monooleate (Table 2). Therefore, similar to sorbitan monooleate, sorbitan sesquioleate and trioleate would not be expected to cause aquatic toxicity at their water solubility limits (WSL).

Based on the ECOSAR-EPIWIN calculations for various HPV sorbitan esters, the ecotoxicity level (LC50 or EC50 value in mg/L) was greater than the chemical's water solubility (mg/L) (Table 2 and 3). These findings would suggest that acute aquatic toxicity would not be expected at the water solubility limits of the sorbitan esters.

Overall, there are sufficient calculated and experimental aquatic toxicity data to cover the range of the sorbitan esters or to support read-across assessment of the substances in this category based on their structural/chemical similarity. The data available (Table 3) appear to in-

dicate that acute aquatic toxicity would not be expected at the water solubility limits of the sorbitan esters. For purposes of the HPV Program, the existing data are sufficient to address the potential aquatic toxicity of the members of the sorbitan esters category and, therefore, no additional aquatic toxicity testing is proposed.

4.4 Mammalian Toxicity Data for Substances in the Sorbitan Esters Category

A) Acute Mammalian Toxicity

Summary of Available Acute Oral Toxicity Data

Acute oral toxicity data relevant to the sorbitan esters category are summarized in Table 3. Five (5) of the 6 HPV sorbitan esters have been adequately tested for acute oral toxicity. In addition, the structurally analogous surrogate sorbitan ester has been adequately evaluated. There were no deaths when these sorbitan esters were administered orally at doses of 2000 mg/kg or greater in rats. Overall, the acute oral LD_{50} for these substances was greater than the 2000 mg/kg, indicating a very low order of toxicity for the sorbitan esters. In addition, the structurally analogous surrogate sorbitan ester also showed similar very low degree of acute oral toxicity.

Data Assessment and Test Plan for Acute Mammalian Toxicity

Adequate acute oral toxicity studies have been conducted for five HPV sorbitan esters and for one structurally analogous surrogate sorbitan ester. The data consistently demonstrate a very low order of acute toxicity for the sorbitan monoesters and sorbitan di-, tri- and tetraesters. No additional acute toxicity testing is proposed for substances in this category. It should be mentioned that additional acute oral and dermal toxicity studies have been carried out and reported for various sorbitan fatty acid esters, which are structurally related to the HPV substances [see reviews by Elder (1985); CIR (1999); Andersen (2002)]; however, they will not be discussed in depth here. The data summarized in the reviews for the sorbitan fatty acid esters by the Cosmetic Ingredient Review expert panel [Elder (1985); CIR (1999); Andersen (2002)] support the very low degree of acute oral and dermal toxicity for the HPV sorbitan esters.

B) Mutagenicity and Genotoxicity

Summary of Mutagenicity and Genotoxicity Data

A summary of the mutagenicity and genotoxicity data for the HPV and the surrogate substances in the sorbitan esters category is presented in Table 3. Bacterial or mammalian gene mutation assays or *in vitro* chromosomal aberration assays have been conducted for these substances. None of the sorbitan esters tested showed any evidence of mutagenic or clastogenic activity, with or without metabolic activation.

Bacterial Gene Mutation Assay

Sorbitan monostearate (CAS 1338-41-6) has been adequately tested in the bacterial reverse mutation assay and has been shown to be negative, with and without metabolic activation. The surrogate structural analogous substance, sorbitan fatty acid C6-10, tetraester (CAS 228573-47-5) also has been evaluated in the bacterial reverse mutation assay and has been shown to be negative, with or without metabolic activation.

In vitro Chromosomal Aberration Assay

Sorbitan monostearate (CAS 1338-41-6) did not cause any chromosomal aberrations in the Syrian golden hamster embryo cell assay and did not show clastogenic activity. Sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5, a surrogate substance) was negative in an *in vitro* human lymphocyte cytogenetics assay, with and without metabolic activation, showed no evidence of clastogenic activity and did not cause chromosomal aberrations.

Data Assessment and Test Plan for Mutagenicity and Genotoxicity

The existing data showed no evidence of mutagenicity or genotoxicity for the tested sorbitan esters. The data from the four studies consistently demonstrated no evidence of mutagenicity or genotoxicity, regardless of metabolic activation. In addition, the existing data should reasonably justify read-across assessments based on the very close structural and chemical similarities (i.e., sorbitan and natural fatty acids) among related sorbitan esters. By bridging these data, the potential genotoxicity of the members of the sorbitan esters category have been adequately addressed for HPV purposes and, therefore, no additional testing is proposed.

C) Repeated-Dose Toxicity

Summary of Repeated-Dose Toxicity Data

Adequate data on repeated-dose toxicity studies are available for the HPV sorbitan esters and structural analogous surrogates of this category. A large number of subchronic oral and dermal studies and chronic oral feeding studies also have been carried out for sorbitan monolaurate, sorbitan monostearate and sorbitan monooleate [Elder (1985); CIR (1999); Andersen (2002)]. It is beyond the scope of this test plan to discuss in detail all the subchronic and chronic toxicity studies for these three sorbitan monoesters. The comprehensive reviews by the Cosmetic Ingredient Review expert panel should be consulted if more detailed information is needed. Some of the repeated-dose oral feeding studies have been summarized in Table 3 and are briefly discussed below.

Repeated-Dose Oral Toxicity

Oral feeding toxicity studies have been carried out in rats for 16 weeks with sorbitan monooleate at dietary concentrations of 0, 2.5, 5 and 10% (Ingram *et al.* 1978). The LOAEL was 2.5% dietary concentration (~1800 mg/kg/day) based on increased kidney weight findings that were considered significant in both male and female rats. In 13-week feeding studies with sorbitan monolaurate in rats, the LOAEL was 2.5% or approximately 2200 mg/kg/day (Cater *et al.* 1978).

In 2-year feeding studies at 5, 10 and 20% in the diet, rats tolerated sorbitan moonostearate (CAS 1338-41-6) with no adverse effects [Oser *et al.* (1957b)]. However, at 20%, there was a small but significant decrease in the growth rates of male rats. Hence, the NOAEL was 10% in the diet in rats based on these findings. In an 80-week dietary study in mice, no adverse effects were observed for sorbitan monostearate at 2% concentration in the diet and the NOAEL was 2% or approximately 2600 mg/kg/day (Hendy *et al.* 1978).

Sorbitan monooleate (CAS 1338-43-8) fed to rats at 5% concentrations in the diet for 2 years showed no adverse effects on growth, hematology, clinical chemistry, survival, organ size or histopathology (ACI, 1970). The NOAEL was reported to be 5% in the diet for sorbitan monooleate in this study.

Repeated dose oral studies have also been carried out with the surrogate substance, sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5). Oral gavage studies for 28 days at dose levels up to 1000 mg/kg /day resulted in no systemic toxicity. No treatment-related effects on mortality were observed. The NOAEL was 1000 mg/kg/day for this sorbitan tetraester (see Table 3).

Data Assessment and Test Plan for Repeated-Dose Toxicity

Sufficient repeated-dose toxicity studies using different animal species and oral and dermal routes of administration have been conducted with sorbitan esters. These data suggest that members of the sorbitan esters category and structurally-related surrogate sorbitan esters exhibit a low order of toxicity following repeated applications and due to their chemical and structural similarities, the existing data should support reasonable justification for bridging data within this HPV category.

By bridging these data, the potential repeated exposure toxicity of members of the sorbitan esters category are adequately addressed, and no additional testing is proposed for the HPV Challenge Program**.**

D) Reproductive/Developmental Toxicity

Summary of Reproductive/Developmental Toxicity Data

A reproductive/developmental (i.e., 4-generation) study of sorbitan monostearate [CAS 1338-41-6] has been reported in the scientific literature. In addition, subchronic toxicity data are available for HPV substances in this category and for the structurally analogous surrogate sorbitan ester that showed no adverse effects to reproductive organs.

Results from the sorbitan monostearate study showed a low order of reproductive/developmental toxicity and are summarized in Table 3.

Reproductive Toxicity

Sorbitan monostearate was administered in the diet at dose levels of 0, 5, 10, and 20 % over a period of two years and over four generations of rats [Oser *et al.* (1956a,b); Oser et al. (1957a,b)]. No effects were observed on growth, food efficiency, reproduction, lactation, metabolism, behavior, mortality, or during gross and histopathological examination of tissues/organs. At the 20% dose level in the diet, newborn mortality was not increased but there were slight effects on growth and impairment of lactation.

It is of interest to note that multigeneration feeding studies have been carried out by MacKensie *et al.* (1986) to evaluate the reproductive and developmental effects of sorbitol. Male and female rats fed up to 10% sorbitol in the diet during the 96-week study had no significant adverse clinical, behavioral, or reproductive effects, and no significant gross or microscopic changes were observed. Sorbitol was also studied indirectly as part of a mixture of hydrogenated starch hydrolysates (HSH), which contained about 7% sorbitol as part of the polyhydric alcohol mixture. The HSH mixture was investigated as part of a two-year ingestion study, a multigeneration reproduction study and a teratology study. At concentrations of 18% in drinking water (3000-7000 mg/kg/day), HSH did not produce reproductive or developmental effects (Modderman, 1993). These results indicate that sorbitol does not cause reproductive/developmental toxicity in animals.

Given these findings, the lack of effects on reproductive organs in this or other subchronic studies with related sorbitan esters and the low order of toxicity of sorbitan monostearate, sorbitol, and natural fatty acids, it seems unlikely that sorbitan esters as a category would present reproductive and developmental toxicity concerns.

Developmental Toxicity/Teratogenicity

As previously discussed, sorbitan monostearate was administered in the diet at dose levels of 0, 5, 10, and 20 % over a period of two years and over four generations of rats [Oser et al. (1956a,b); Oser et al. (1957a,b)]. No effects were reported on growth, reproduction, lactation, behavior, mortality, or during gross and histopathological examination of tissues/organs. At the 20% dose level in the diet, newborn mortality was not increased but there were slight effects on growth and impairment of lactation. Multigeneration feeding studies with sorbitol or with sorbitol as part of a mixture of polyhydric alcohols in hydrogenated starch hydrolysate (HSH) did not report developmental effects in animals [Mackensie *et al.* (1986); Modderman (1993)]. From these findings, it appears unlikely that sorbitan esters, as a category, would pose developmental toxicity concerns.

Data Assessment and Test Plan for Reproductive/Developmental Toxicity

Sorbitan monostearate (CAS 1338-41-6) has been reported in the scientific literature not to cause reproductive and development effects in a 4-generation study in rats. In addition, subchronic toxicity studies with various sorbitan esters in this HPV category [e.g., CAS 1338-39-2; CAS 1338-41-6; CAS 1338-43-8] and with a structural analogous surrogate (i.e., CAS 228573-47-5), have been shown not to adversely affect (i.e., gross observations, histopathology) the reproductive organs. These available reproductive/developmental toxicity data, in conjunction with reproductive/developmental data for sorbitol and natural fatty acids support reasonable justification for bridging data gaps within this HPV category. For purposes of the HPV Program, these data are considered adequate to address the potential developmental/reproductive toxicity of sorbitan esters and no additional developmental/reproductive toxicity tests are proposed.

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that adequate health effects and toxicity data exist for the sorbitan esters category of the aliphatic esters and for other structurally analogous surrogate sorbitan esters to substantially characterize the mammalian health effects, aquatic toxicity and biodegradation endpoints for all the members of this category under the HPV program (Table 4). No additional toxicity tests for the above toxicity endpoints are proposed for the sorbitan esters category of the aliphatic esters. Thus, the resourceful use of the existing data will help to minimize the use of animals for testing and at the same time adequately assess the potential hazards of the substances in the sorbitan esters category under the HPV Program.

Table 4. Assessment Plan for Substances in the Sorbitan Esters Category under the HPV Program

		Mammalian Health Effects						Ecotoxicity - Biodegradability			
Sorbitan Ester	MW	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Sorbitan, monolaurate	346	√	√	R	R	√	R	√	R	R	√
Fatty acids, coco, mono-esters with sorbitan	346-374	R	R	R	R	R	R	R	R	R	R
Sorbitan, monooleate	429	√	√	R	R	√	R	√	R	R	√
Sorbitan, monostearate	431	√	√	√	√	√	√	R	R	R	R
Sorbitan, sesquioleate	569	√	R	R	R	R	R	R	R	R	R
* Sorbitan, fatty acids, C6-10, tetraester	668	√	√	√	√	√	--	√	√	√	√
Sorbitan, trioleate	958	√	R	R	R	R	R	R	R	R	R

* Shaded (highlighted) areas denote surrogate substance - its data are included in table to help bridge data for structurally analogous HPV sorbitan ester.

-- Denotes that no data for specific toxicity endpoint heading has been located for this surrogate sorbitan ester.

Abbreviations in table:
√ = adequate existing data available
R = read-across data from structurally analogous sorbitan esters to bridge data

Adequate calculated and experimental data for physicochemical properties (i.e., melting point, boiling point, vapor pressure, water solubility and octanol-water partition coefficient) exist for the sorbitan esters in this category. No further testing is proposed for these endpoints for the sorbitan esters category of the aliphatic esters.

In addition, there are adequate experimental or calculated data for environmental fate endpoints such as biodegradability (see below), photodegradation, hydrolysis and chemical distribution in the environment (via fugacity modeling) for the sorbitan esters. No further testing is proposed for these endpoints for the sorbitan esters category.

Adequate aquatic toxicity and biodegradability data exist for both the HPV sorbitan esters and one structurally analogous surrogate sorbitan ester to sufficiently cover the range of sorbitan esters within in this category. The very close structural and chemical similarities between the homologous sorbitan esters within this category reasonably justify and support read-across assessments to

bridge data gaps among the HPV substances. No further aquatic toxicity and biodegradability testing are proposed for the sorbitan esters category of the aliphatic esters.

Robust summaries of existing health effects, environmental fate and effects, and physicochemical properties data are attached in the Appendix. Summaries of other environmental fate endpoints are also included. Existing data for the surrogate structurally analogous sorbitan esters are either included in robust summaries or are referenced in the Appendix should they have been reviewed or summarized previously (e.g., SIDS, comprehensive reviews by the Cosmetic Ingredient Review expert panel, BIBRA Toxicity Profiles). This test plan is expected to provide adequate information to substantially characterize the mammalian health effects, physicochemical properties and environmental fate and effects (including aquatic toxicity, biodegradability) endpoints for the sorbitan esters category of the aliphatic esters under the HPV Chemical Challenge Program.

6.0 REFERENCES *

Andersen FA (2002). Final report on the safety assessment of sorbitan caprylate, sorbitan cocoate, sorbitan diisostearate, sorbitan dioleate, sorbitan distearate, sorbitan isostearate, sorbitan olivate, sorbitan sesquiisostearate, sorbitan sesquistearate, and sorbitan triisostearate. Int. J. Toxicol. **21 (Suppl. 1):** 93-112.

Atlas Chemical Industries (ACI) (1970). Summaries of toxicological data. Lifespan feeding studies on sorbitan monolaurate and sorbitan mono-oleate. Food Cosmet. Toxicol. 8: 339-340 (1970). Summary of data from Toxicology Report on Span 20 and Span 80 (ACI Studies).

Bevan C (2001a). Monohydric Alcohols - C1 to C6 *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 77, pp. 365-460. J. Wiley & Sons, New York.

Bevan C (2001b). Monohydric Alcohols - C7 to C18, Aromatic and other alcohols. *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 78, pp. 461-541. J. Wiley & Sons, New York.

BIBRA (1990). Toxicity profile for sorbitan monostearate. British Industrial Biological Research Associaton (BIBRA).

BIBRA (1994). Toxicity profile for sorbitan trioleate. British Industrial Biological Research Association (BIBRA).

Bisesi MS (2001). Esters of mono- and alkenyl carboxylic acids and mono- and polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 79, pp. 543-633, J. Wiley & Sons, New York

Buchwald P (2001). Structure-metabolism relationship: steric effects and the enzymatic hydrolysis of carboxylic esters. Mini. Rev. Med. Chem. **1:** 101-111.

Cater BR, Butterworth KR, Gaunt IF, Hoosan J, Grasso P and Gangoli SD (1978). Short-term toxicity study of sorbitan monolaurate (Span 20) in rats. Food Cosmet. Toxicol. **16:** 519-526.

CIR (Cosmetic Ingredient Review) (1999). Final Report Addendum. Safety assessment of sorbitan caprylate, sorbitan cocoate, sorbitan diisostearate, sorbitan dioleate, sorbitan distearate, sorbitan isostearate, sorbitan olivate, sorbitan sesquiisostearate, sorbitan sesquioleate, and sorbitan tiisostearate. Cosmetic Ingredient Review. Washington, DC (1999). June 14, 1999, pp. 1-28.

Cragg ST (2001a). Aliphatic carboxylic acids, saturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 70, pp. 689-787. J. Wiley & Sons, New York.

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* The list of references is not a comprehensive bibliography of the literature for the HPV sorbitan esters substances or related surrogates. Pertinent papers cited in the text are those that are important in health hazard assessments or for toxicity data bridging for structurally similar surrogate sorbitan esters. The information and data in the papers and reviews supplement the robust summaries developed for the toxicology studies of the HPV substances, which are ultimately used to address the SIDS toxicity endpoints for the sorbitan esters in this HPV test plan.

Cragg ST (2001b). Aliphatic carboxylic acids, unsaturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 71, pp. 789-861. J. Wiley & Sons, New York.

David RM, et al.(2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri-, or polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 6, Chapter 80, pp. 635-932. J. Wiley & Sons, New York.

Eisenhard WC (1999). Esterification *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 139-152.

Elder RL (1985). Final report on the safety assessment of sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate, and sorbitan trioleate, J. Amer. Coll. Toxicol. **4 (3):** 65-121.

Elder RL (1986). Final report on the safety assessment of coconut oil, coconut acid, hydrogenated coconut acid and hydrogenated coconut oil. J. Amer. Coll. Toxicol. **5 (3):** 103-121.

Elder RL (1987). Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. J. Amer. Coll. Toxicol. **6:** 321-401.

EPIWIN (1999). Estimation Program Interface for Windows. Version 3.02. Syracuse Research Corp., Syracuse, New York, USA.

Fitzhugh OG, Bourke AR, Nelson AA, Frawley JP (1959). Chronic oral toxicities of four stearic acid emulsifiers. Toxicol. Appl. Pharmacol. **1:** 315-331.

Hendy RJ, Butterworth KR, Gaunt IF, Kiss IS, Grasso P (1978). Long-term toxicity study of sorbitan monostearate (Span 60) in mice. Food Cosmet Toxicol. **16:** 527-534.

Heyman E (1982). Hydrolysis of carboxylic esters and amides in Metabolic Basis of Detoxification (Jakoby WB, Bend JR, Caldwell J (eds.), Academic Press, New York, pp. 229-245

High Production Volume (HPV) (2001). See HPV chemical categories [e.g., tall oil fatty acids and related substances (CAS 61790-12-3); tall oil fatty acid is comprised of 48% oleic and 35% linoleic acids] submitted to U.S. EPA.

Ingram AJ, Butterworth KR, Gaunt IF, Grasso P and Gangoli SD (1978). Short-term toxicity study of sorbitan mono-oleate (Span 80) in rats. Food Cosmet. Toxicol. **16:** 535-542.

IUCLID (1996-2003). International Union Chemical Information Database, European Chemicals Bureau Existing Chemicals. Data hedset for each chemical found by CAS number or chemical name.

Klimisch H, Andreae M, Tillman U (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. **15:** 1-5.

Leinweber FJ (1987). Possible physiological roles of carboxylic ester hydrolases. Drug Metab. Rev. **18:** 379-439.

Mackay D, DiGuardo A, Paterson S, Cowan CE (1996). Evaluating the environmental fate of a variety of types of chemicals using the EQC model. Environ. Toxicol. Chem. **15:** 1627-1637.

MacKensie KM, Hauck WN, Wheeler AG, Roe FJC (1986). Three-generation reproduction study of rats ingesting up to 10% sorbitol in the diet - and a brief review of the toxicological status of sorbitol. Food Chem. Toxicol. **24:** 191-200.

Modderman JP (1993). Safety assessment of hydrogenated starch hydrolysates. Regul. Toxicol. Pharmacol. **18:** 80-114.

Monick JA (1968). Alcohols: Their Chemistry, Properties and Manufacture. Reinhold Book Corp., New York.

Oser BL, Oser M (1956a). Nutritional studies on the diets containing high levels of partial ester emulsifiers. I. General plan and procedures: growth and food utilization. J. Nutrit. **60:** 367

Oser BL, Oser M (1956b). Nutritional studies on the diets containing high levels of partial ester emulsifiers. II. Reproduction and lactation . J. Nutrit. **60:** 489-505.

Oser BL, Oser M (1957a). Nutritional studies on the diets containing high levels of partial ester emulsifiers. III. Clinical and metabolic observations. J. Nutrit. **61:** 149.

Oser BL, Oser M (1957b). Nutritional studies on the diets containing high levels of partial ester emulsifiers. IV. Mortality and post-mortem pathology: general conclusions. J. Nutrit. **61:** 235.

Parkinson A (2001). Biotransfromation of xenobiotics: (hydrolysis) in Casarett & Doull's Toxicology: The Basic Science of Poisons (Klassen CD, ed.), McGraw-Hill, New York, pp. 137-142.

Patty's Toxicology, 5th edition. Bingham E, Cohrssen B, Powell C (editors). 8-Volumes. J. Wiley & Sons, New York (2001).

Randles SJ (1999). Esters *in* Synthetic Lubricants and High Performance Functional Fluids (2nd ed.), Rudnick LR and Shubkin RL (eds.), Marcel Dekker, New York, pp. 63-101.

RTECS (Registry of Toxic Effects of Chemical Substances (2001). National Institute for Occupational Safety and Health of the U.S. Department of Health and Human Services. Health hazard and toxicity data for individual chemical was found by CAS number or chemical name.

Satoh T, Hosokawa M. (1998). The mammalian carboxylesterases: from molecules to functions. Ann. Rev. Toxicol. Pharmacol. **38:** 257-288.

Swisher RD (1987). Surfactant Biodegradation (2nd ed.), Marcel Dekker, New York, pp. 728-729; 826-827.

Testa B, Mayer J.(2003). Hydrolysis in Drug and Product Metabolism: chemistry, biochemistry and enzymology, J. Wiley, New York, 800 pp.

Thurman RG, Kauffman FC (eds.)(1992). Alcohols and Esters. Volume 3 in Ethel Browning's Toxicity and Metabolism of Industrial Solvents (2nd Ed.), Snyder R (Series Editor), Elsevier, Amsterdam.

U.S. EPA (1999a). Determining the adequacy of existing data. OPPT, EPA.

U.S. EPA (1999b). The use of structure-activity relationships (SAR) in the High Production Volume (HPV) Chemical Challenge Program. OPPT. EPA.

Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals (3rd ed.), Wiley, New York.

Wick AN, Joseph L (1953). The metabolism of sorbitan monostearate. Food Res. **18:** 79

7.0 List of Tables and Figures

Table 2. Summary Table of Physicochemical Properties and Environmental Fate Data for the Sorbitan Esters

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (mm Hg@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Chemical Distribution (Transport) within Environmental Compartments- Fugacity Model			
											Soil %	Air %	Water %	Sediment %
18	346	1338-39-2	Sorbitan, monolaurate	176 c	462 c	9.34 E-12 c	3.15 c	13.19 c	0.20 c	14.2 c	68.2 c	0.04 c	31.4 c	0.3 c
18-20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	176-191 c	462-485 c	1.1-9.3 E-12 c	3.15-4.14 c	1.29-13.2 c	0.19-0.20 c	7.7 - 14.2 c	64.6-68.2 c	0.04-0.3 c	31.4-33.4 c	0.3-1.8 c
24	429	1338-43-8	Sorbitan, monooleate	223 c	535 c	1.03 E-14 c	5.89 c	0.0191 c	0.05 c	2.2 c	37.2 c	0.1 c	15.6 c	47.1 c
24	431	1338-41-6	Sorbitan, monostearate	222 c	531 c	1.38 E-14 c	6.10 c	0.0122 c	0.17 c	7.7 c	36.2 c	0.3 c	12.6 c	50.9 c
33	569	8007-43-0	Sorbitan, sesquioleate	248 c	609 c	6.83 E-17 c	10.11 c	5.93 E-07 c	0.04 c	0.90 c	28.6 c	0.1 c	7.2 c	64.1 c
38	669	228573-47-5	Sorbitan, Fatty Acid C6-10 Tetraester	< -25C 266 c	>295 C 636 c	1.7 E-07 Pa at 25 C 1.87 E-14 c	>7.7 11.57 c	<0.02 7.37 E-09 c	0.19 c	0.79 c	32.1 c	0.5 c	10.7 c	56.7 c
60	958	26266-58-0	Sorbitan, trioleate	350 c	916 c	1.32 E-19 c	21.71 c	5.97 E-19 c	0.02 c	0.59 c	27.4 c	0.0 c	3.5 c	69.1 c

Highlighted row denotes substance that was not on the HPV list for the Sorbitan Esters category but that was included in table to facilitate group evaluation or for bridging purposes due to their chemical/structural similarities as sorbitan esters.

c = calculated data using EPWIN; all other values in table are derived from measurements or data obtained from company reports, documents, MSDS, reference handbooks, secondary literature sources.

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data may not accurately reflect melting points for these substances.

** = many of the substances have boiling points determined under reduced pressure and some values may have been extrapolated to one atmosphere.

Table 3. Summary Table of Mammalian Health Effects, Ecotoxicity and Biodegradation Data for the Sorbitan Esters

				Mammalian Health Effects						Ecotoxicity and Biodegradation			
Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Reproductive Toxicity	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50 (mg/L)	Daphnia EC50 or EL50 (mg/L)	Algal EC50 or EL50 (mg/L)	Biodegradation %
18	346	1338-39-2	Sorbitan, monolaurate	33.6 g/kg >39.8 g/kg 41.25 g/kg	13-wk Feeding Study (Rat) LOAEL ~2200 mg/kg (2.5% diet)			Subchronic toxicity study has not been shown to adversely affect reproductive organs		75 mg/L Aq. Tox would not be expected at WSL **	> WSL *		Not Readily Biodeg. 60% in 28 days OECD 301C
18 - 20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)								> WSL *		
24	429	1338-43-8	Sorbitan, monooleate	> 39.8 g/kg	16-wk Feeding Study (Rat) LOAEL ~1800 mg/kg/d (2.5% diet) 2-year Feeding Study (Rat) NOAEL (5%diet)			Subchronic toxicity study has not been shown to adversely affect reproductive organs		> 1000 mg/L Aq. Tox would not be expected at WSL **	> WSL *	> WSL *	Not Readily Biodeg. 62% in 28 days OECD 301C
24	431	1338-41-6	Sorbitan, monostearate	> 15.9 g/kg	80-wk Feeding Study (Mice) NOAEL 2% diet (~2600 mg/kg/d) 2-Yr Feeding Study (Rat) NOAEL 5% diet	Negative (Ames)	Negative (Hamster embryo cells in vitro)	In 2-yr , 4-generation feeding study in rats, no effects were observed on reproduction, gestation, growth, lactation, mortality at 5 and 10% in the diet. At 20% in diet, slight effects on growth and impairment of lactation.	In 2-yr , 4-generation feeding study in rats, no effects were observed on reproduction, gestation, growth, lactation, mortality at 5 and 10% in the diet. At 20% in diet, slight effects on growth and impairment of lactation.		> WSL *	> WSL *	
33	569	8007-43-0	Sorbitan, sesquioleate	> 39.8 g/kg							> WSL *	> WSL *	
38	668	228573-47-5	Sorbitan, fatty acids C6-10, tetraester	>2.0 g kg	28-Day Oral Gavage Study NOAEL 1000 mg/kg (rat)	Negative (Ames)	Negative (human lymphocyte in vitro)	Subchronic toxicity study has not been shown to adversely affect reproductive organs		>1000 mg/L Aq. Tox would not be expected at WSL **	>1000 mg/L Aq. Tox would not be expected at WSL **	>1000 mg/L Aq. Tox would not be expected at WSL **	Readily Biodeg. 83.1% in 28 days OECD 301B
60	958	26266-58-0	Sorbitan, trioleate	> 39.8 g/kg									

Highlighted row denotes read-across data from non-HPV sorbitan ester that was included in Table in order to help facilitate category evaluation and for bridging purposes for HPV sorbitan esters due to their chemical/structural similarities.

* > WSL signifies that the calculated ecotoxicity value (LC50 or EC50) (mg/L) was greater than the chemical's water solubility limit (WSL) (mg/L). ECOSAR-EPIWIN was used to calculate the aquatic toxicity LC50 or EC50 value of the chemical in fish, daphnia or algae.
In some cases, ECOSAR was not able calculate the ecotoxicity with reasonable uncertainty for a specific aquatic tox endpoint (fish, daphnia or algae) due to water solubility limitations of the chemical or water solubility restrictions of the specific model.

** Actual exp. LC50 or EC50 value (nominal loading rate) was many times greater than water solubility limit (WSL) of the chemical. Therefore, aquatic toxicity would not be expected at the WSL (water solubility limit) of the test material.